UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/931,506	08/16/2001	Shannon Mitchell	2002906-0002	3684

22907 7590 08/26/2004

BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 08/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/931,506	MITCHELL ET AL.	
	Examiner	Art Unit	
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *148,185,188-190,194,196-198 and 219-269* is/are pending in the application.

4a) Of the above claim(s) *219* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *148,185,188-190,194,196-198,220-242,244-246,248-251 and 254-269* is/are rejected.

7)☒ Claim(s) *243,247,252 and 253* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/14/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a reply to the Paper filed 28 May 2004 in response to the Non-Final Office Action mailed 29 December 2003. Claims 148, 185, 188-190, 194 and 196-198 were considered in the 29 December Office Action. Claims 148, 185, 188-190, 194 and 196-198 were amended and claims 219-269 were added in the 28 May Paper. Claims 148, 185, 188-190, 194, 196-198 and 219-269 are pending.

Election/Restrictions

Newly submitted claim 219 is directed to an invention that is independent or distinct from the invention originally elected for the following reasons: The claim is directed to a method for producing a decellularized tissue engineered construct, which is the subject matter of non-elected restriction Group I (20 December 2002 and 31 March 2003 Office Actions).

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 219 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted, however, that claim 219 is directed to a method of making the product presently under examination. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final

rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 148, 185, 188-190, 194, 196-198 and 220-269 are presently under consideration.

Response to Amendment

Claim Rejections - 35 USC § 102

Rejection of claim 148 under 35 U.S.C. 102(b) as being anticipated by Bruchman *et al.* (1995) WO 95/29712 (hereinafter Bruchman '712), Bruchman *et al.* (1997) WO 97/46266 (hereinafter, Bruchman '266) or Bruchman *et al.* (March 1999) U.S. Patent No. 5,879,383 (hereinafter, Bruchman '383) is withdrawn.

Claims 185, 189, 190, 194, 196 and 197 stand rejected under 35 U.S.C. 102(b) as being anticipated by either one of Bruchman '266 or Bruchman '383 for reasons of record and herein below in the response to arguments.

Claim Rejections - 35 USC § 103

Claims 188 and 198 stand rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Bruchman '266 or Bruchman '383 for reasons of record and herein below in the response to arguments.

Response to Arguments

In response to rejection of claims 185, 188-190, 194 and 196-198 under 35 U.S.C. §102(b) or §103(a) as anticipated by or obvious over Bruchman '266 or Bruchman '383, Applicant has amended the claims such that they depend from newly added claims 255, which is directed to a decellularized tissue engineered construct comprising a 3-demensional proteinaceous extracellular matrix synthesized by a first population of cells grown *in vitro* on a substrate whereby a proteinaceous extracellular matrix surrounding said cells is formed; and a

second population of cells, wherein the decellularized tissue engineered construct is seeded with the second population of cells.

Applicant alleges that the claims are now distinguished from the art because neither Bruchman '266 nor Bruchman '383 teaches that the tissue engineered construct comprises "a proteinaceous extracellular matrix" and that the matrix is formed "surrounding said cells." This argument has been fully considered but is not deemed persuasive because, given the broadest reasonable interpretation of the limitations of claim 255 in light of the specification, the tissue engineered construct of Bruchman '266 nor Bruchman '383 comprises all of the structural limitations of the claimed construct.

In support of the limitation "3-dimensional proteinaceous extracellular matrix", Applicant cites the passage at paragraph 81 of the published application (Pub. No.: US 2002/0115208 A1) which reads, "[t]hese references disclose techniques for establishing a three-dimensional matrix, **inoculating the matrix with the desired cells**, and maintaining the culture. In general, a tissue engineered construct is produced by seeding cells onto an appropriate substrate and culturing the cells under conditions suitable for growth. The substrate can be flat, tubular, or, in general, **can be configured to assume any desired three-dimensional shape**. For example, the substrate may be formed into shapes including but not limited to spheres, ellipsoids, [etc.]." The statement cited by Applicant, viewed in context, appears to be describing a three-dimensional (*i.e.,* non-planar) construct provided by seeding cells on a matrix (*i.e.*, substrate) of some defined 3-dimensional shape. The skilled artisan would not construe the statement as describing a "3-dimensional proteinaceous extracellular matrix".

Applicant additionally cites Fig. 5A as showing the proteinaceous extracellular matrix surrounding the cells prior to decellularization and Fig. 5 B as showing the matrix after decellularization. Although the images cited do appear to show a proteinaceous extracellular matrix having 3-dimensions, it should be noted that Bruchman '266 and Bruchman '383 also teach that their tissue engineered constructs comprise a proteinaceous extracellular matrix (see *e.g.* Bruchman '266, page 19, second full paragraph) and one of ordinary skill in the art would expect the subendothelial extracellular matrix of Bruchman '266 and Bruchman '383 to have 3 dimensions as that term is commonly understood (*i.e.*, height, width and length).

Anticipation of the 3-dimensional extracellular proteinaceous extracellular matrix of the instant claims by the endothelial cell matrix of Bruchman '266 and Bruchman '383 is further evidenced by claim 248 of the instant application, which recites that the 3-dimensional proteinaceous extracellular matrix of claim 220 is formed by endothelial cells.

Finally, in addition to the proteinaceous endothelial cell basement membrane, the tissue engineered construct of Bruchman '266 and Bruchman '383 also comprises the 3-dimensional proteinaceous extracellular matrix synthesized by a first population of vascular smooth muscle cells (see especially Figure 6 and the caption thereto) which is the same as the extracellular matrix depicted in Figure 5 of the instant application. Thus, the decellularized tissue engineered construct of Bruchman '266 and Bruchman '383 does, in fact, comprise a 3-dimensional proteinaceous extracellular matrix synthesized by a first population of cells grown *in vitro* on a substrate whereby a proteinaceous extracellular matrix surrounding the cell is formed. Therefore, the limitation does not distinguish the claimed invention from the decellularized tissue

engineered construct of Bruchman '266 and Bruchman '383 and Applicant's arguments, as a whole, are not deemed persuasive.

New Grounds Necessitated by Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 222 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The MPEP states, "[i]f new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. §112, first paragraph-written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." (MPEP § 2163.06). The MPEP further states, "[w]henever the issue arises, the fundamental factual inquire is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in the application" (*Id.*, § 2163.02). The introduction of claim changes which involve

narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996).

The instant claim 222 is directed to a decellularized tissue engineered construct maintained under conditions suitable for growth of the cells for a period of time sufficient for formation of a tissue engineered construct having a thickness of greater than 200 μm. In support of these limitations, Applicant cites Fig. 6A, which is alleged to show a cross-section of a construct having a thickness of >200μm. However, Fig. 6, which is described in Example 5, actually shows a cross section through a segment of native adult porcine carotid artery seeded with vascular smooth muscle cells. Comparing the fluorescent image of the vascular smooth muscle cells (Fig. 6B) with the contrast view of Fig. 6A shows that only a small fraction of the thickness of the construct is provided by the cultured cells and that the vessel itself was greater than 200 μm before the cells were seeded. Clearly, therefore, the smooth muscle cells of Fig. 6A were not responsible for "formation of a tissue engineered construct having a thickness of greater than 200 μm" and the original disclosure provides no support for a tissue engineered construct of greater than 200 μm formed by cells maintained under conditions of growth for any period of time. Therefore, the limitations of claim 222 constitute new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 231-233 and 240 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 231-233 are indefinite in the recitation of "the biologically active agent". There is no antecedent basis for a biologically active agent in claim 220, from which the claims depend.

Claim 240 is indefinite in the reciting, "the length of tubing". There is no antecedent basis for a length of tubing in claim 220, from which claim 240 depends.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 220, 223-226, 238-242, 244, 246, 248 and 249 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman *et al.* (1995) WO 95/29712 (hereinafter Bruchman '712).

Bruchman '712 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which is subsequently subjected to decellularization (see especially page 6, paragraph 5; page 8, third full paragraph; and page 14, second full paragraph). For reasons of record and in the "Response to Arguments" herein, the decellularized tissue engineered construct of Bruchman '712 anticipates the decellularized tissue engineered construct of independent claim 220. Bruchman '712 further teaches the decellularized tissue engineered construct wherein: at least 80% of the cells are removed by decellularization according to claims 223-226 (see especially page 14, line 26); the substrate comprises a synthetic polymer length of tubing coated with vascular smooth

muscle cells according to claims 238-242, 244 and 246 (see espccially page 10 and the second full paragraph on page 11); and comprises at least two different cell types according to the limitations of claims 248 and 249 (see especially paragraph 1 and 2 on page 16).

The decellularized tissue engineered construct taught by Bruchman '712 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '712.

Claims 220, 223-226, 230-233, 238-242, 244, 246, 248-250, 254, 255, 258, 259, 261, 263, 264, 268 and 269 are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman '266 (*supra*) as evidenced by BD Biosciences description of Endothelial Cell Growth Supplement (previously made of record).

Bruchman '266 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which is subsequently subjected to decellularization (see especially the paragraph bridging pages 7 and 8). For reasons of record and in the "Response to Arguments" herein, the decellularized tissue engineered construct of Bruchman '266 anticipates the decellularized tissue engineered construct of independent claim 220. Bruchman '266 further teaches the decellularized tissue engineered construct wherein: at least 80% of the cells are removed by decellularization according to claims 223-226 (see especially page 19, first full paragraph); the substrate comprises a synthetic polymer length of tubing coated with vascular smooth muscle cells according to claims 238-242, 244 and 246 (see especially the second full paragraph on page 14 and the first full paragraph on page 15); and comprises at least two different cell types according to the limitations of claims

248 and 249 (see especially the third full paragraph on page 23 and the second full paragraph on page 24).

Bruchman '266 also teaches the tissue engineered construct further comprises a biologically active agent (page 8, lines 9-10) selected from an agent to enhance recellularization (i.e., RGD; see especially Example 8), a pharmaceutical composition (see especially Example 6) and other agents (see especially page 12, third full paragraph) according to the limitations of claims 230-233.

Bruchman '266 further teaches embodiments wherein the biologically active agent is a cell according to the limitations of claim 255 (see especially page 12, third full paragraph) wherein: the decellularized tissue engineered construct has been treated with a growth factor and serum during a first growth period according to claims 258, 259, 268 and 269 (see especially the formulation of ECGM in the second full paragraph on page 17 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); and the decellularized tissue engineered construct is produced using cells according to claim 261 and 263 (see especially the second full paragraph on page 24); and the construct is maintained for growth period under conditions suitable for growth of the population of cells according to claim 264 (page 7, fifth full paragraph).

The limitations of claims 250 and 254 are product by process limitations, which do not distinguish the claims from the products disclosed by Bruchman '266. *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) states: "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the

product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

There is no evidence of record that the construct produced using neonatal cells (claim 250), which encompasses neonatal vascular smooth muscle and endothelial cells, would be different from the construct produced according to the teachings of Bruchman '266. Further, the limitation that the construct be produced with genetically transformed cells, recited in claim 254, does not distinguish the claimed product because many genetically transformed cells would produce a construct that is the same as the construct described by Bruchman '266. For example, a tissue engineered construct produced using a vascular smooth muscle cell transformed to express a protein that is not secreted and is not involved in synthesis of extracellular matrix proteins would not be different from tissue engineered construct produced using an untransformed cell. Therefore, claim 254 still reads on the decellularized tissue engineered construct of Bruchman '266.

The tissue engineered construct taught by Bruchman '266 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '266.

Claims 220, 223-225, 238-242, 244-246, 248-250, 254, 255, 259, 260, 261-264, 268 and 269, are rejected under 35 U.S.C. 102(b) as being anticipated by Bruchman '383 (*supra*) as evidenced by BD Biosciences description of Endothelial Cell Growth Supplement.

Bruchman '383 teaches a tissue engineered construct comprising a substrate seeded with cells and maintained under conditions suitable for growth of the cells for a growth period which

is subsequently subjected to decellularization (see especially columns 5, 7 and 13). For reasons of record and in the "Response to Arguments" herein, the decellularized tissue engineered construct of Bruchman '383 anticipates the decellularized tissue engineered construct of independent claim 220.

Bruchman '383 further teaches the decellularized tissue engineered construct wherein: at least 80% of the cells are removed by decellularization according to claims 223-226 (see especially column 17); the substrate comprises a synthetic polymer length of tubing or a flat surface coated with vascular smooth muscle cells according to claims 238-242 and 244-246 (see especially columns 14 and 15); and comprises at least two different cell types according to the limitations of claims 248 and 249 (see especially column 18).

Bruchman '383 further teaches embodiments wherein the decellularized construct is seeded with a cell according to the limitations of claim 255 (see especially columns 5 and 17-18) wherein: the decellularized tissue engineered construct has been treated with a growth factor and serum during a first growth period according to claims 258, 259, 268 and 269 (see especially the formulation of ECGM in column 16 and the description of Endothelial Cell Growth Supplement from BD Biosciences (formerly Collaborative Biomedical Products)); the decellularized tissue engineered construct is produced using cells according to claim 261 (see especially column 18); the population of cells is autologous vascular endothelial cells according to claims 262 and 263 column 5, lines 30-32); and the construct is maintained for growth period under conditions suitable for growth of the population of cells according to claim 264 (see especially column 5, line 45).

The limitations of claims 250 and 254 are product by process limitations, which do not distinguish the claims from the products disclosed by Bruchman '383 (*Id.*) There is no evidence of record that the construct produced using neonatal cells (claim 250), which encompasses neonatal vascular smooth muscle and endothelial cells, would be different from the construct produced according to the teachings of Bruchman '383. Further, the limitation that the construct be produced with genetically transformed cells, recited in claim 254, does not distinguish the claimed product because many genetically transformed cells would produce a construct that is the same as the construct described by Bruchman '383 (*Id.*). Therefore, claim 254 still reads on the decellularized tissue engineered construct of Bruchman '383.

The tissue engineered construct taught by Bruchman '383 is the same as the tissue engineered construct taught in the instant application; therefore the limitations of the claims are met by Bruchman '383.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 220 and 228-230 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Bruchman '712 (*supra*), Bruchman '266 (*supra*) or Bruchman '383 (*supra*).

The teachings of Bruchman '712, Bruchman '266 and Bruchman '383 with regard to claim 220 are described herein above. The art of record thus teaches all of the limitations of the dependent claims 139-141 except for a decellularized tissue engineered construct wherein least 90%, 95% or 99% are removed (claims 228-230 respectively). The limitations of claims 228-230 would, however, have been obvious to the ordinary skilled artisan based on the teachings of each of the citations alone because each of Bruchman '712, Bruchman '266 and Bruchman '383 teaches that scanning electron microscopy of representative samples confirmed nearly total loss of the native endothelium (see

especially Bruchman '712 third full paragraph on page 14; Bruchman '266, page 19; and Bruchman '383, column 17).

Claims 220 and 251 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchman '266 and Bruchman '383 as applied to claim 220 above.

Claim 251 is directed to a construct comprising a decellularized tissue engineered construct and a population of cells, wherein the decellularized tissue engineered construct is produced using human cells. As described above, Bruchman '266 and Bruchman '383 teach a decellularized tissue engineered construct that is produced with vascular endothelial cells. Although Bruchman '266 and Bruchman '383 do not explicitly teach that the constructs should be made using human cells, the limitation would be obvious to one of ordinary skill in the art at the time the invention was made. Both Bruchman '266 and Bruchman '383 teach that the decellularized tissue engineered constructs described therein are to be used as vascular prostheses to be used in humans (see, e.g., the Abstracts). Further, one of ordinary skill in the art would know that it is desirable to use homotypic cells and tissues in the manufacture of the decellularized tissue engineered constructs in order to avoid the immune response that is typically elicited by xenotypic cells and tissues (see, *e.g.*, Bruchman '383, column 18, lines 3-5). Thus, the ordinary skilled artisan would have both the knowledge and motivation to use human cells in the manufacture of the constructs of Bruchman '266 and Bruchman '383. Therefore, the invention of claim 251, as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 148, 220, 221 and 234-237 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bruchman '712 as applied to claim 220 above, and further in view of Niklason *et al.* (1999) *Science* 284:489-493 (previously made of record).

Bruchman '712 teaches all of the limitations of the claims except for a tissue engineered construct that has been subjected to a mechanical force or pulsatile stimulus during a first growth period and a growth period of about 6 to 8 weeks. Bruchman '712 teaches that the tissue engineered constructs produced are to be used as vascular prostheses. Niklason *et al.* teaches a method of producing tissue engineered constructs similar to the tissue engineered constructs taught by Bruchman '712 (see especially the caption of Figure 1) and that culturing the constructs under pulsatile conditions produced superior results. In the third column on page 490, Niklason *et al.* teaches that vessels cultured under pulsatile conditions for 8 weeks had a histologic appearance more similar to that of native arteries. In the middle column on page 491, Niklason *et al.* teaches that vessels grown without pulsatile stress possessed significantly less collagen and reduced suture retention strengths. In the middle column of page 492, Niklason *et al.* teaches that smooth muscle cells cultured under pulsatile conditions appear to be more highly differentiated and thus less prone to hyperplasia. Finally, in the paragraph bridging pages 492 and 493 and the first full paragraph on page 493, of Niklason *et al.* teaches that pulsed grafts remained open for 4 weeks *in vivo* while nonpulsed grafts developed thrombosis after 3 weeks.

It would have been obvious to one of ordinary skill in the art at the time the instant application was filed to modify the teachings of Bruchman '712 to include the 8 week pulsatile culture conditions of Niklason *et al.* in order to produce a superior graft. The teachings from Niklason *et al.* provide the motivation to combine the teachings because the constructs taught by

Bruchman '712 are intended to be used as vascular grafts and Niklason *et al.* teaches that pulsatile culture conditions produce superior grafts. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because production of the decellularized construct according to the method of Bruchman '712 is not dependent upon the method by which the tissue engineered construct is established.

Although, Bruchman '712 does not teach electrical stimulation according to claim 148, the electrical stimulation of the claim is a process limitation which must result in a product having properties that are different from those of the prior art to be patentable (*Id.*). In the instant case, the electrical stimulation is not limited to any particular amount or duration of stimulation. Therefore, it is more likely than not that the claim encompasses embodiments that are no different from the constructs made with no electrical stimulation at all. Therefore, the construct of Bruchman '712 in view of Niklason *et al.* is the same as the instant claimed construct.

Claims 148, 220, 221, 234-237, 255-257, 260 and 264-267 are rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Bruchman '266 (*supra*) or Bruchman '383 (*supra*), as applied to claims 220, 255, 251 and 264 above, in view of Niklason *et al.* (*supra*).

Bruchman '266 and Bruchman '383 teach all of the limitations of the claims except for a tissue engineered construct that has been subjected to a mechanical force or pulsatile stimulus during a first growth period and a growth period of about 6 to 8 weeks. Bruchman '266 and Bruchman '383 teach that the tissue engineered constructs produced are to be used as vascular prostheses. As described above, Niklason *et al.* teaches a method of producing tissue engineered constructs similar to the tissue engineered constructs taught by Bruchman '266 and Bruchman

'383 and that culturing the constructs for 8 weeks under pulsatile conditions produced superior results. It would have been obvious to one of ordinary skill in the art at the time the instant application was filed to modify the teachings of Bruchman '266 or Bruchman '383 to include the pulsatile culture conditions of Niklason *et al.* in order to produce a superior graft. The teachings from Niklason *et al.*, set forth above, provide the motivation to combine the teachings because the constructs taught by Bruchman '266 and Bruchman '383 are intended to be used as vascular grafts and Niklason *et al.* teaches that pulsatile culture conditions produce superior grafts. Absent evidence to the contrary, one would have a reasonable expectation of success in combining the teachings because production of the decellularized construct according to the method of Bruchman '266 or Bruchman '383 is not dependent upon the method by which the tissue engineered construct is established.

Although, Bruchman '266 and Bruchman '383 do not teach electrical stimulation according to claim 148, the electrical stimulation of the claim is a process limitation which must result in a product having properties that are different from those of the prior art to be patentable (*Id.*). In the instant case, the electrical stimulation is not limited to any particular amount or duration of stimulation. Therefore, it is more likely than not that the claim encompasses embodiments that are no different from the constructs made with no electrical stimulation at all. Therefore, the construct of Bruchman '712 in view of Niklason *et al.* is the same as the instant claimed construct.

Allowable Subject Matter

Claims 243, 247, 252 and 253 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Thursday 6:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636